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Desmosome

Making Connections: Desmoplakin as an Intermediate Filament-Binding Protein

Andrew P. Kowalczyk[1] and Margaret D. Kottke[1]

[1]Departments of Cell Biology and Dermatology, Emory University, Atlanta, Georgia, USA.

Correspondence: Dr Andrew P. Kowalczyk, akowalc@emory.edu

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Early work on desmosome morphology and biochemical composition laid the groundwork for the utilization of molecular biological approaches in the 1990s. Important breakthroughs included the cloning and sequencing of the desmoplakin gene, the identification of desmoplakin as an intermediate filament-binding protein and the realization that desmoplakin was part of a family of filament-binding proteins now known as the plakin family of cytolinkers (reviewed in Kowalczyk *et al*., 1999; Leung *et al*., 2002). Collectively, these studies form an important foundation for our understanding of how intermediate filaments associate with the plasma membrane and other cytoskeletal networks.

Green *et al*. (1988), at Northwestern University in Chicago, first isolated and analyzed the desmoplakin coding sequence, which allowed for structural analysis of the amino-acid sequence of the desmoplakin protein (Green *et al*., 1990). From this work, desmoplakin was predicted to harbor a central alpha-helical coiled-coil domain similar to that found in intermediate filaments. This region of desmoplakin would thus encode a rod-like domain connecting globular amino- and carboxy-terminal domains. In addition, the carboxy-terminal domain harbored several interesting features, including the presence of a 38-amino-acid repeated homology domain that was also present in the 230-kDa bullous pemphigoid antigen (BPAG1). The periodicity of charged amino acids within these carboxy-terminal repeats was similar to that found in the 1B rod domain of intermediate filament proteins, leading to the prediction that the desmoplakin carboxyl terminal domain might interact with intermediate filaments. More recent studies have revealed several different means of desmoplakin–intermediate filament interactions, but this early study by Green and colleagues made two major predictions that were substantiated by further studies. First, that desmoplakin and BPAG1 were part of a gene family, and second, that the carboxy-terminal region of this family of proteins might confer intermediate filament binding activity.

Using the desmoplakin cDNA and structural information from the 1990 study as a foundation, along with emerging information about BPAG1 and plectin as intermediate filament-associated proteins, Stappenbeck and Green used molecular biological approaches to define desmoplakin domains functionally (Stappenbeck and Green, 1992; Stappenbeck *et al*., 1993). The most striking finding of their studies was that the desmoplakin carboxy-terminal domain aligned along intermediate filament networks when expressed transiently in cultured cells. These studies demonstrated that the desmoplakin carboxy-terminal domain was both necessary and sufficient for interacting with intermediate filaments, and, when overexpressed, could alter intermediate filament organization. Subsequent studies by the Fuchs laboratory demonstrated that the desmoplakin intermediate filament interactions were direct (Kouklis *et al*., 1994). These findings thereby complemented the structural studies of the desmoplakin gene and were followed by numerous additional biochemical, structural, and yeast genetic approaches (two-hybrid), confirming that the desmoplakin carboxyl terminus is an intermediate filament-binding domain (reviewed in Kowalczyk *et al*., 1999).

Subsequent studies in the late 1990s as well as current studies continue to build upon the foundation initiated by the pioneering discoveries of desmoplakin and plakin family structure. The desmoplakin amino-terminal domain was found to target desmoplakin to desmosomes through associations with armadillo proteins such as plakoglobin and plakophilins. Collectively, these studies revealed the modular nature of desmoplakin and the mechanisms by which it couples filaments to sites of tight cell–cell adhesion. Current studies are focused on the regulation of these interactions and the dynamic properties of desmoplakin in the assembly of adhesive structures (Godsel *et al*., 2005).

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